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# Some Unanswered Questions in Membrane Science

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# We mostly look under the Lamp Post

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**Scientists are conservative and gregarious…**

**...but Nature is mostly empty and unexplored.**

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# Interesting questions don't have to be "discovered". They are already there.

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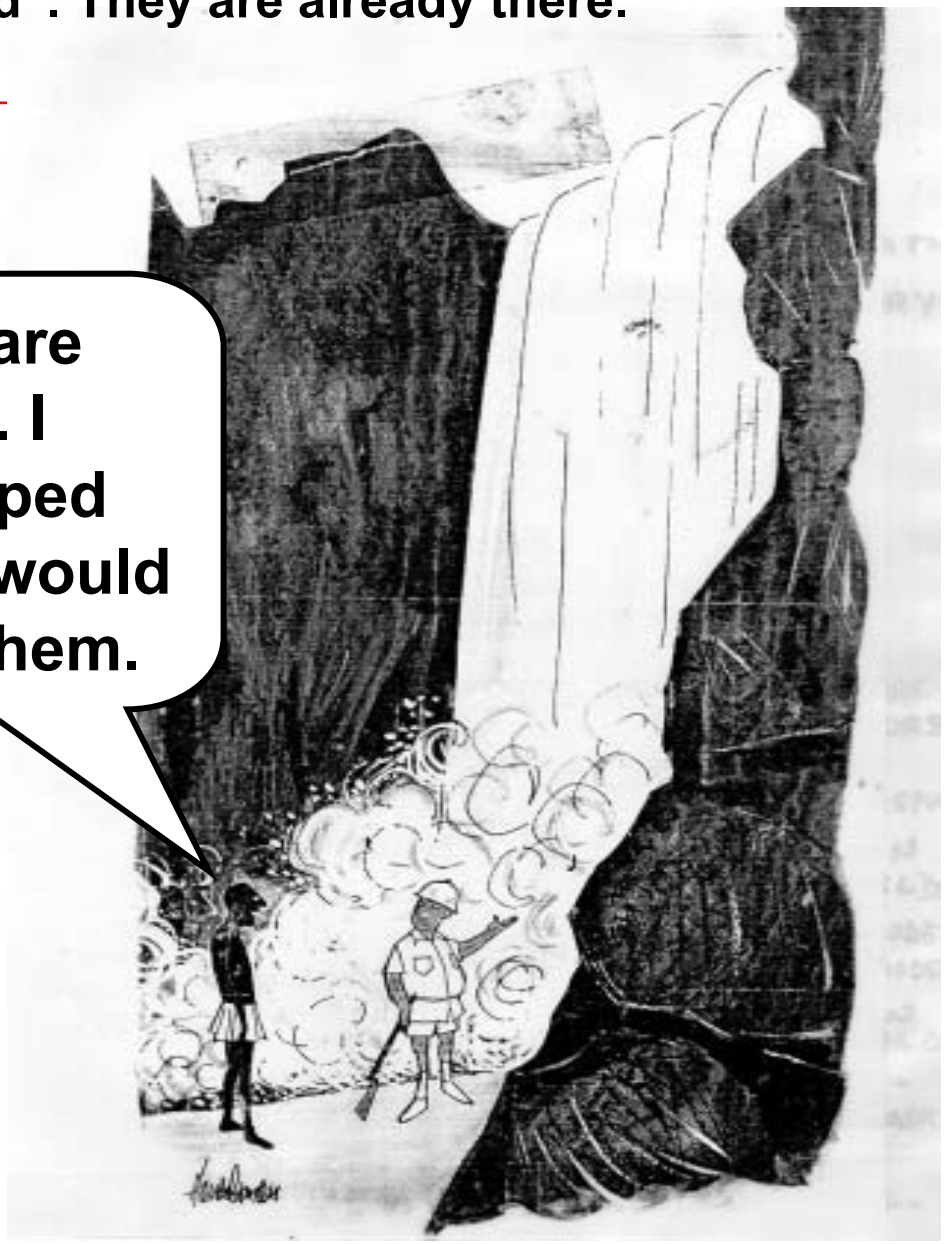

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# Let's start with biomembranes. They are important.

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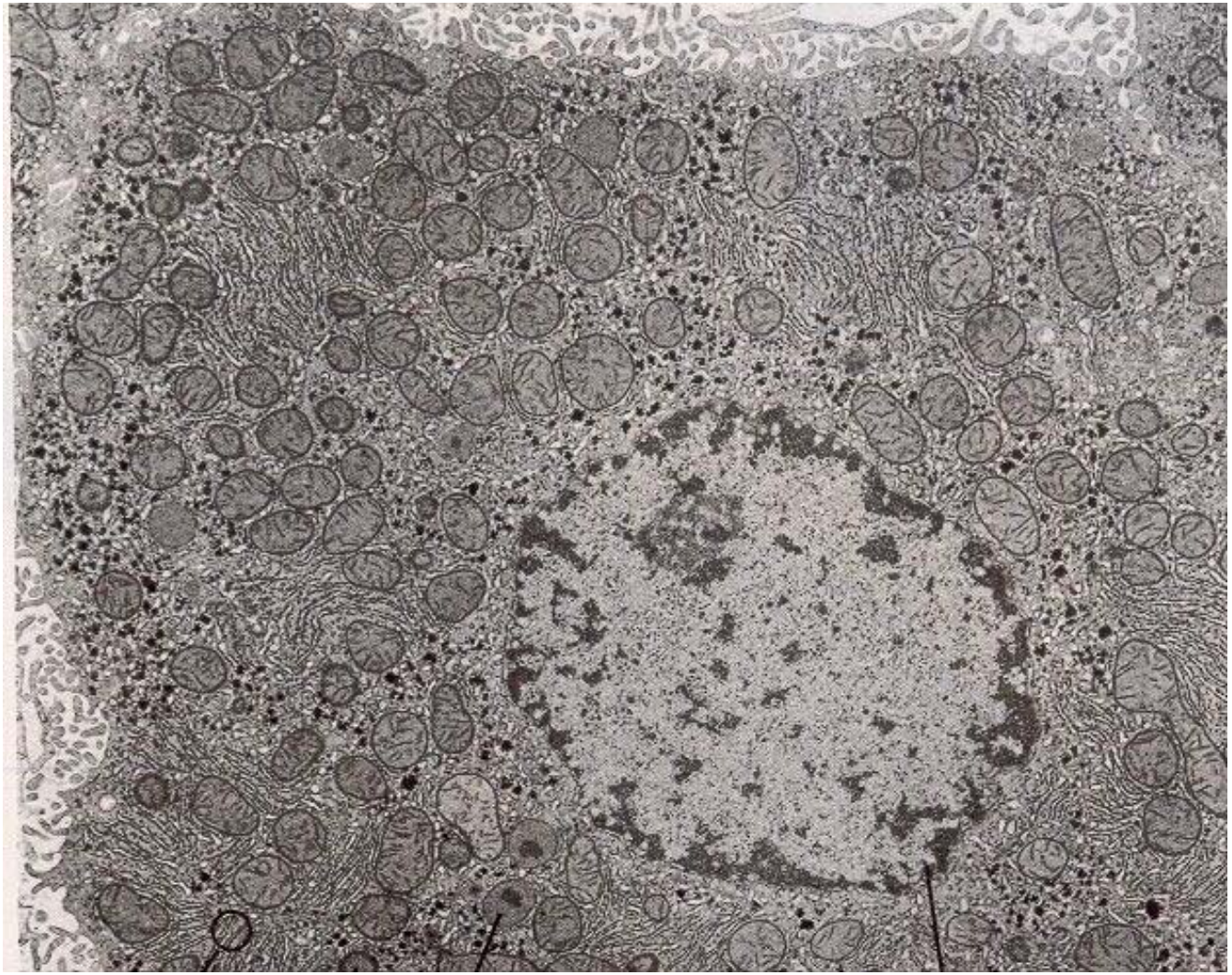

**Rat Hepatocyte**

Lehninger

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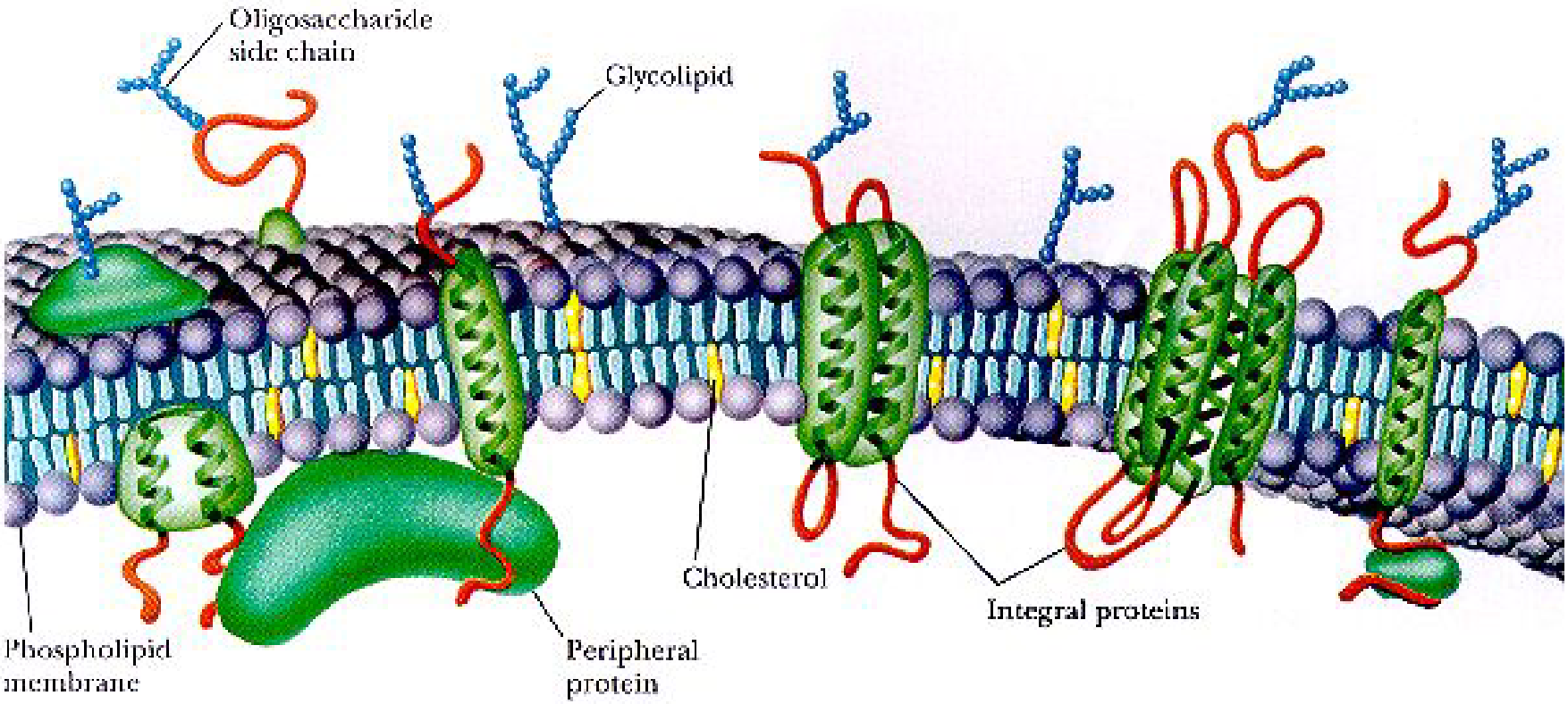
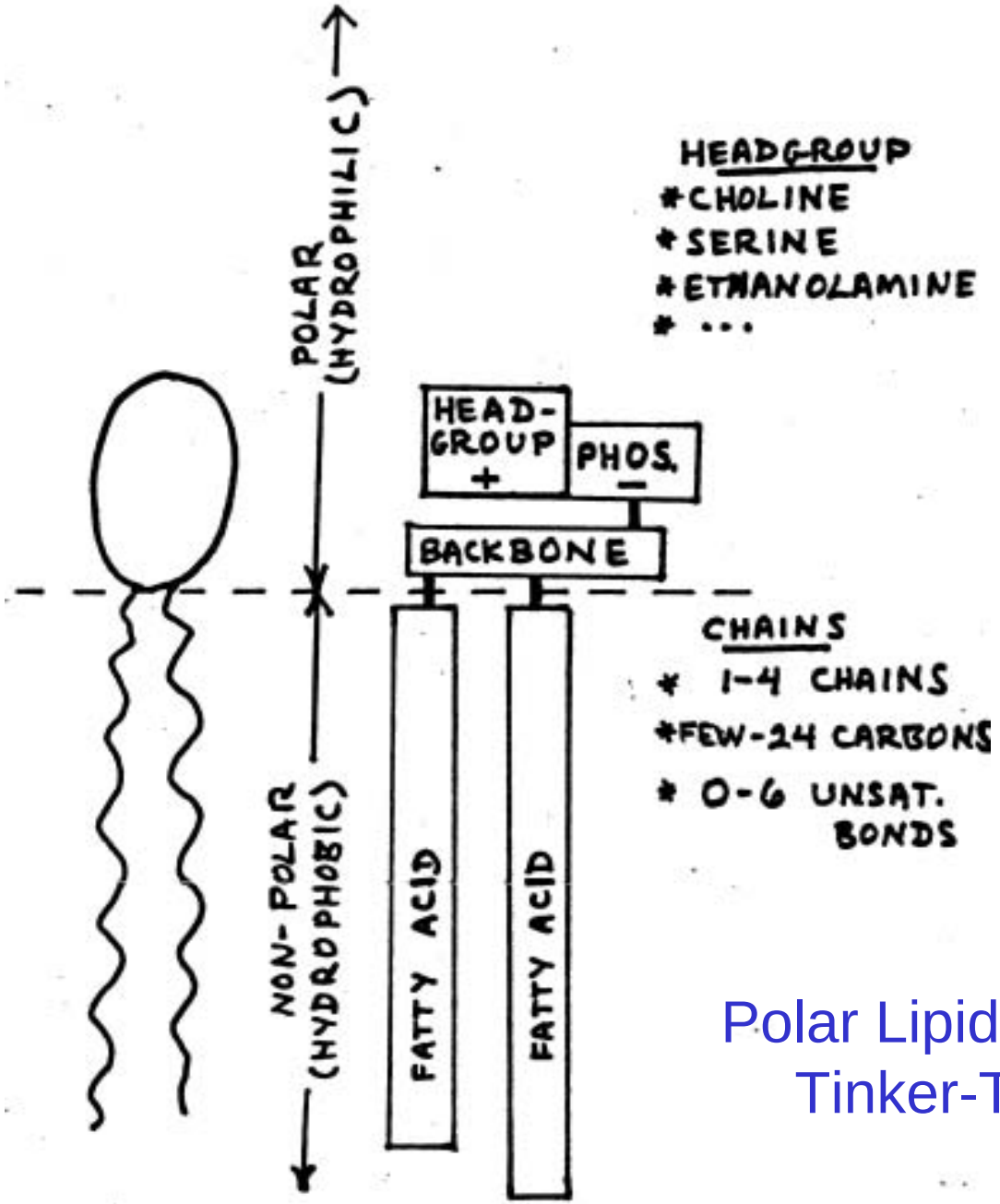



Garrett & Grisham



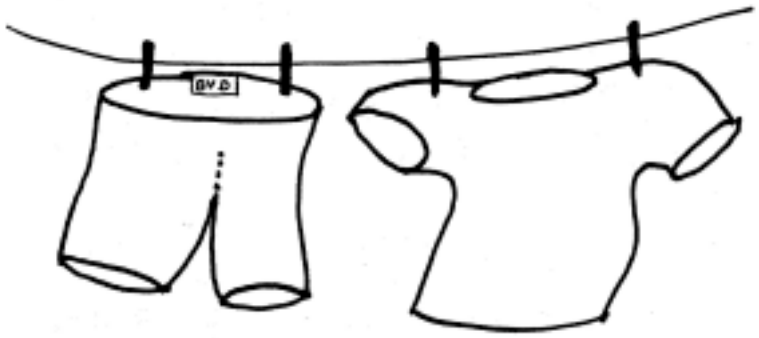

Polar Lipids are like Tinker-Toys.

# Question #1:

## Why are there so many kinds of lipids?

**and**

## How does nature decide which lipids to insert into biomembranes, i.e., what rules are being used?

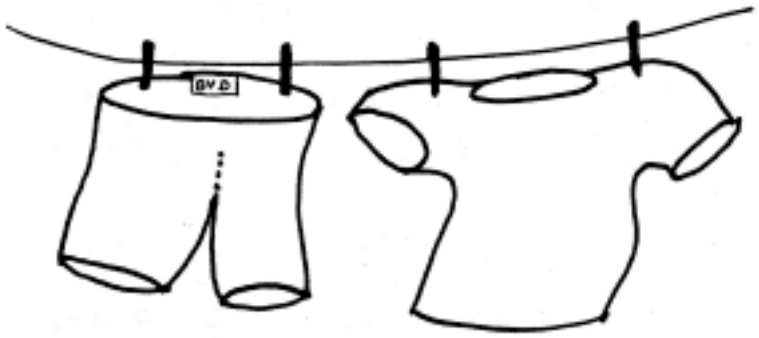


**“Phospholipids prefer to form bilayer structures in aqueous solution....Phospholipid bilayers form rapidly and spontaneously when phospholipids are added to water, and they are stable structures in aqueous solution.”**

***Biochemistry*, Garrett & Grisham**

**“Phospholipids and glycolipids are key membrane constituents because they readily form extensive bimolecular sheets.”**

***Biochemistry*, Stryer**



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*Biochemistry*, Garrett & Grisham

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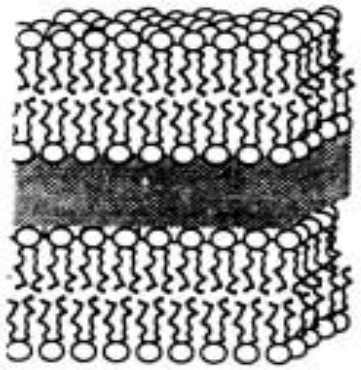
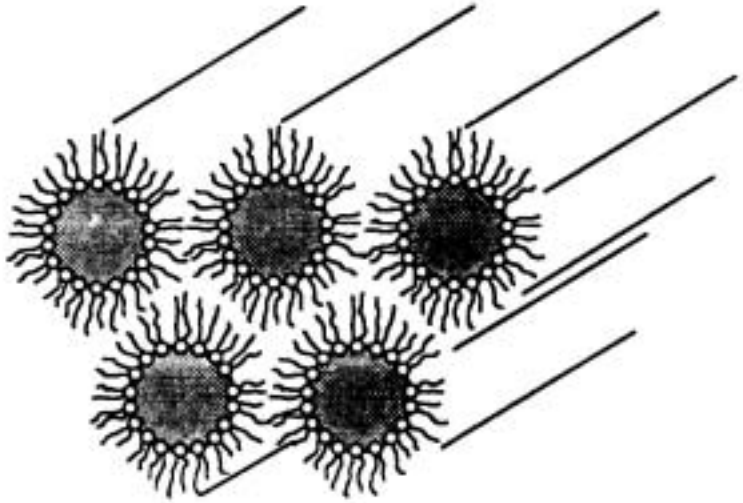
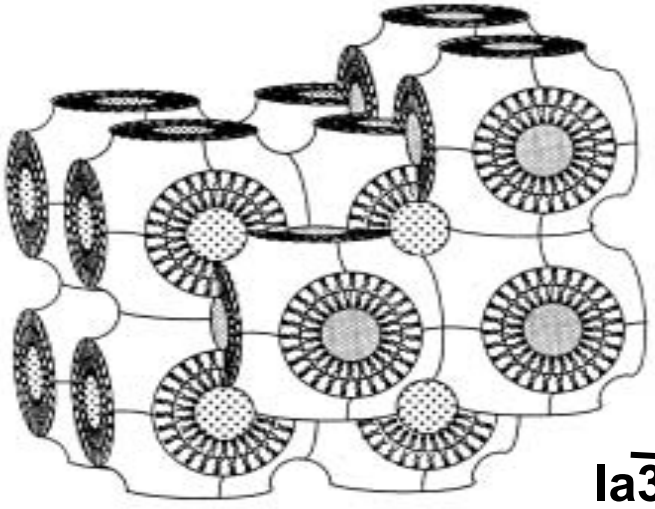
**It ain't so! If biomembrane lipids are isolated into chemically pure species and mixed with water, many lipid phases are observed, with phase transitions vs. T or composition.**



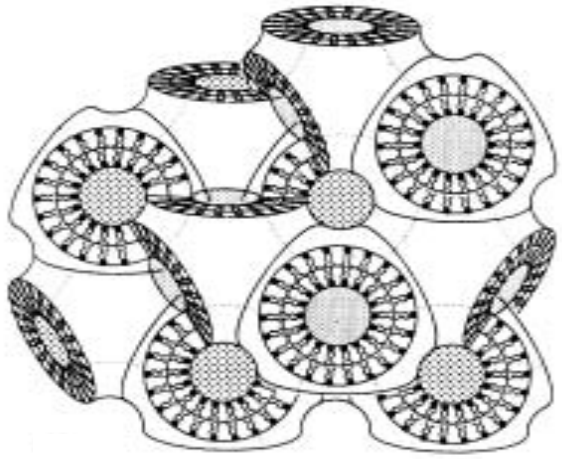
Bilayer Lα



Inverted hexagonal $H_{II}$



$Ia\bar{3}d$



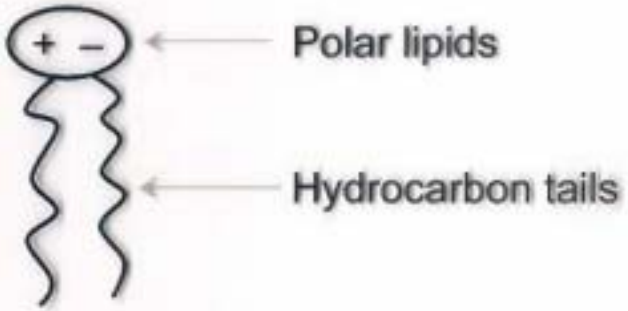
$Pn\bar{3}m$

**A broader perspective comes from "complex fluids" science, which also provides the connection to "membrane" science in the sense of this workshop.**

## Generalized Amphiphile


Where A & B do not mix

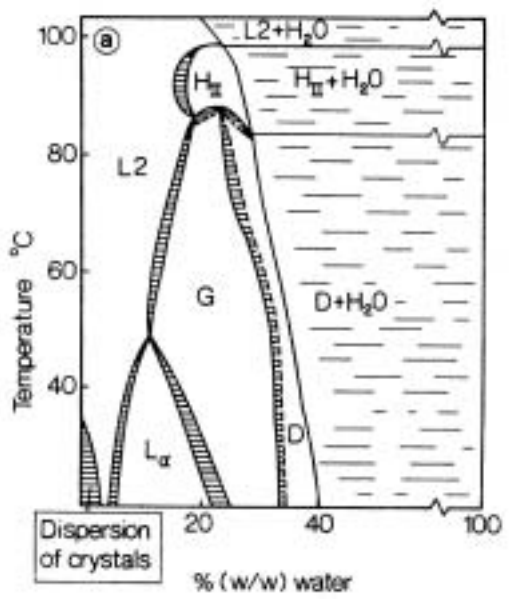
- ***Surfactants***
  - Detergents
  - Soaps
  - Biomembrane lipids




- ***Block copolymers***

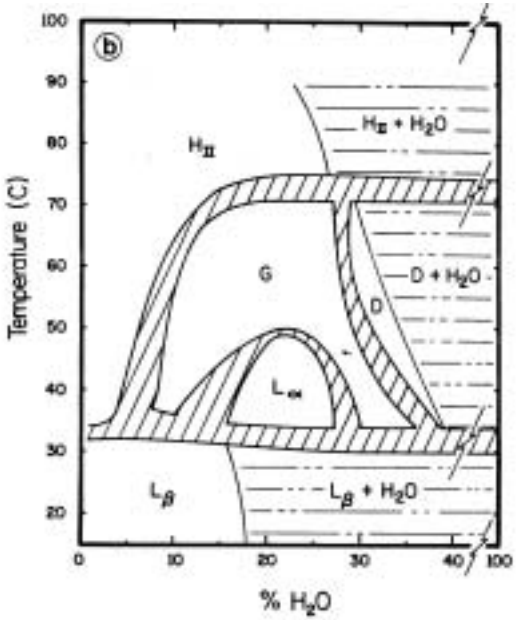
# Question #2:

# Given a chemical structure of an amphiphile, how can we predict the detailed phase diagram?




Glycerol Mono-oleate

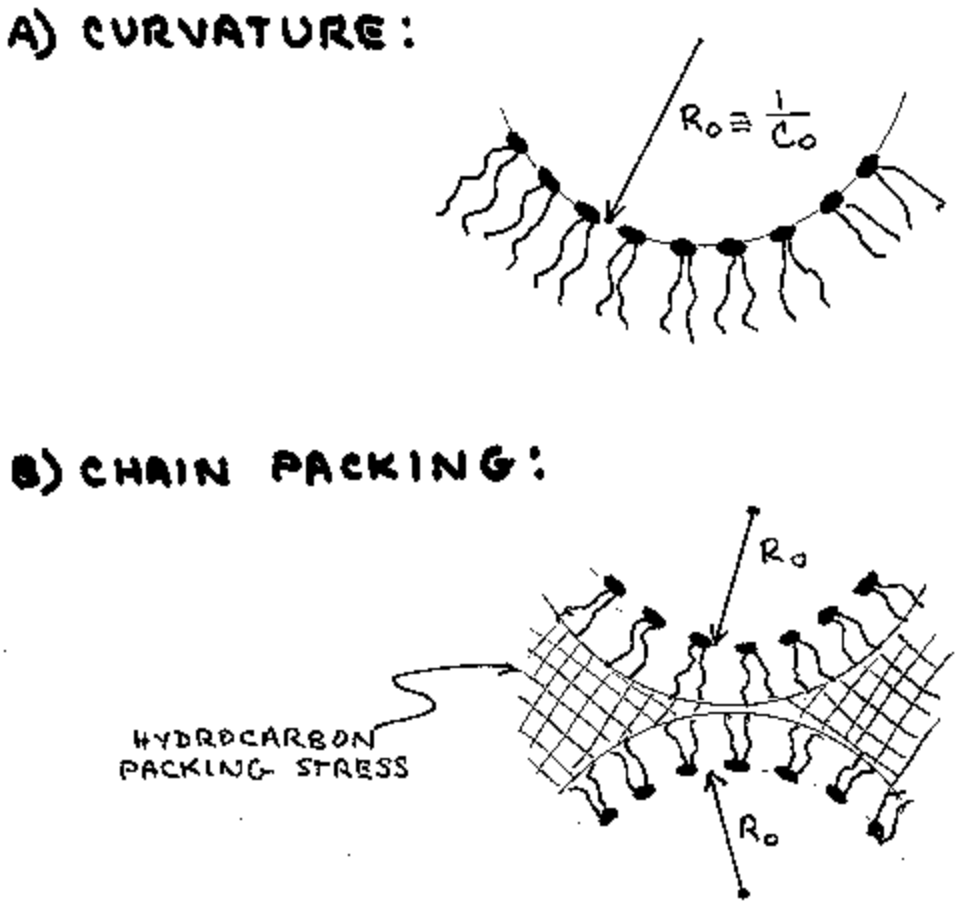
Hyde et al., 1984.




di-12:0 alkyl-glucopyranosyl-*rac*-glycerol

Turner et. al, 1992

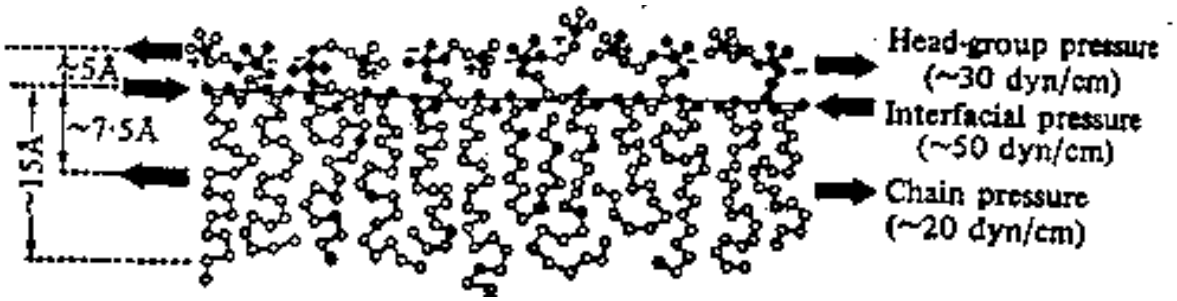
# Competition between monolayer curvature and hydrocarbon chain packing dominates the lipid phase behavior.




See: Kirk et al., *Biochem*. 23 (1984) 1093; Gruner, *J. Phys. Chem.* 93 (1989) 7562.

# CURVATURE

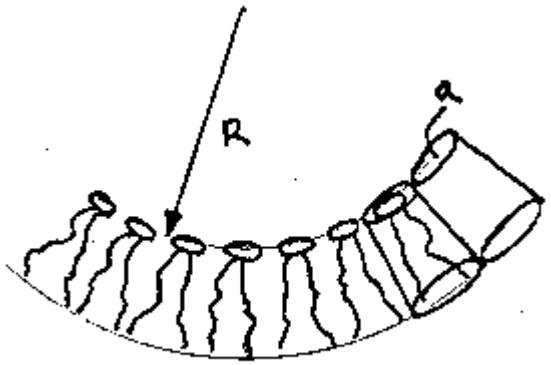
## WATER SIDE




## OILY SIDE

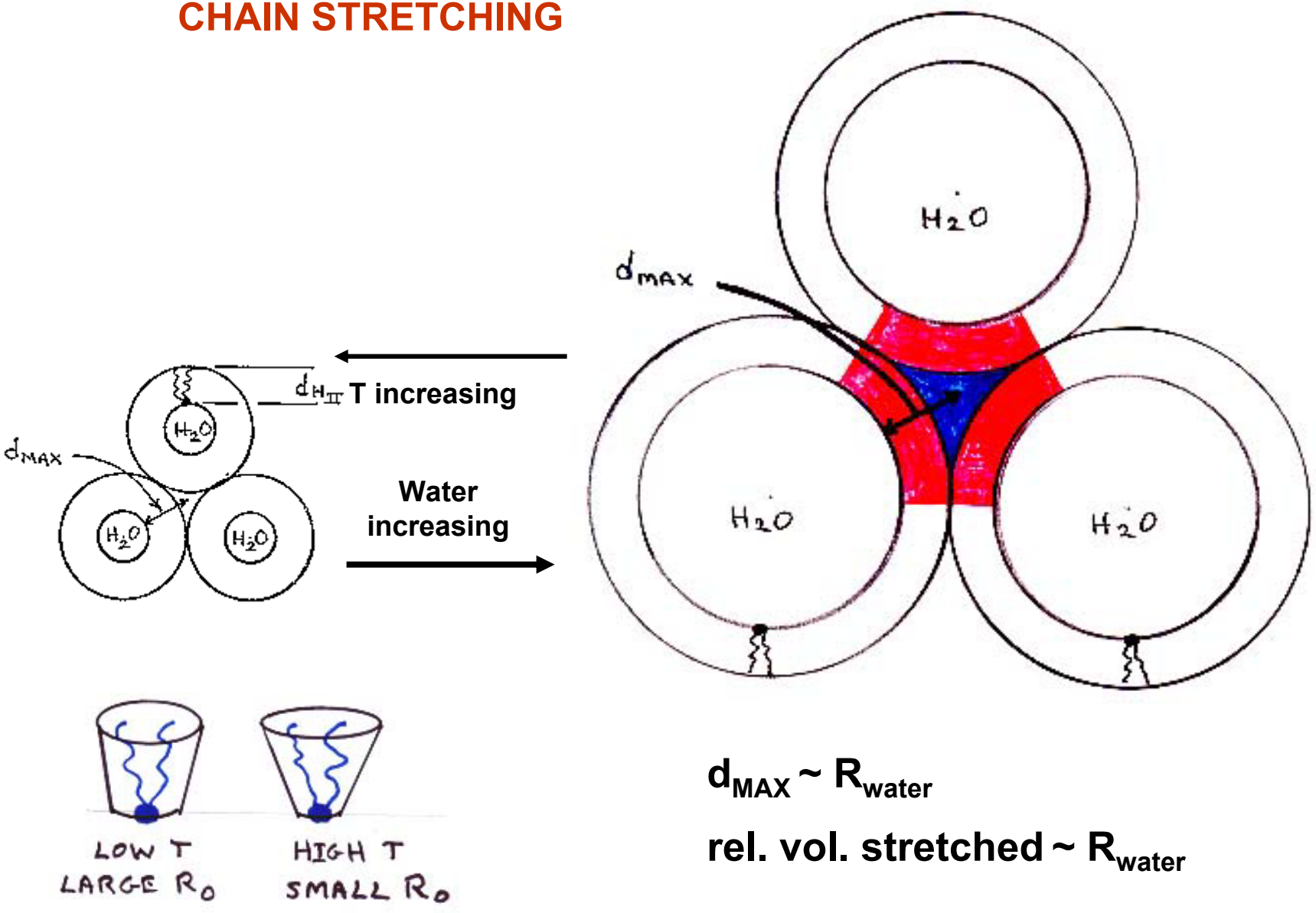
Israelachvili et al., *Quart. Rev. Biophys*. 13 (1980) 121.

Net lateral pressure = 0, but this does not mean the relaxed surface is flat.




$$\mu_{elastic} = (k/2)(1/R - 1/R_0)^2 + \text{const.}$$

# CHAIN STRETCHING




$d_{MAX} \sim R_{water}$

rel. vol. stretched $\sim R_{water}$

- A simple model based on a frustrated competition between lipid monolayer curvature and hydrocarbon chain packing free energies has been amazingly good at predicting and explaining much of the phase behavior of lipid-water dispersions.
- SAXS has been the primary technique for these studies.

**Similar reasoning, with additional considerations of interfacial energies, have been shown to explain much of block copolymer behavior.**

**But a better explanation would require another talk, so let's get back to biomembrane lipids....**

# Real biomembrane lipid layers don't like to be flat!

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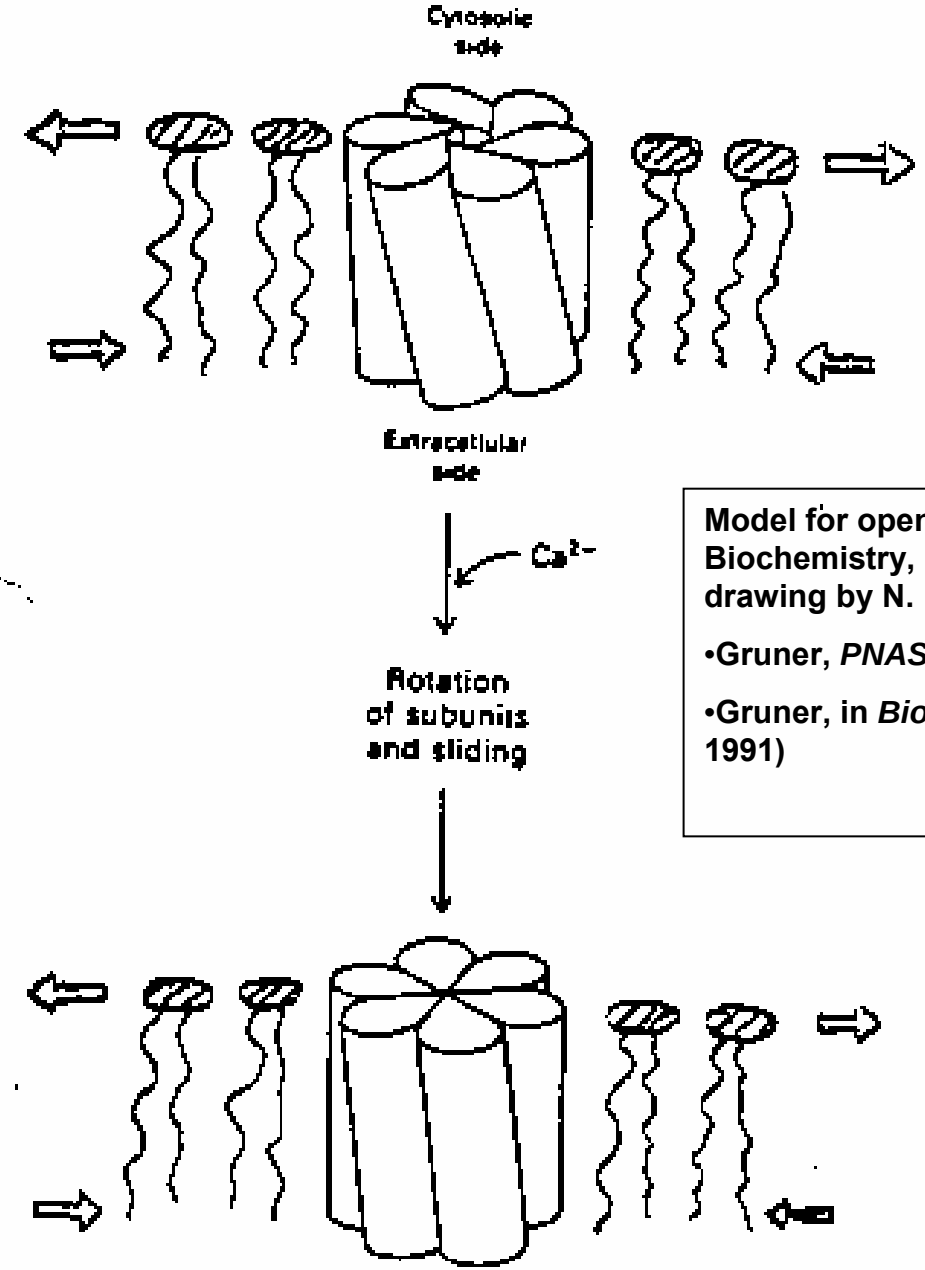
## Question #3:

**Does Nature use biomembrane lipid composition to regulate lipid monolayer spontaneous curvature?**

## Question #4:

**If so, why? To regulate integral membrane protein function?**




**Model for opened and closed states of gap junction. From Biochemistry, L. Stryer (W.H. Freeman, NY 1988) after a drawing by N. Unwin & G. Zampighi. See:**

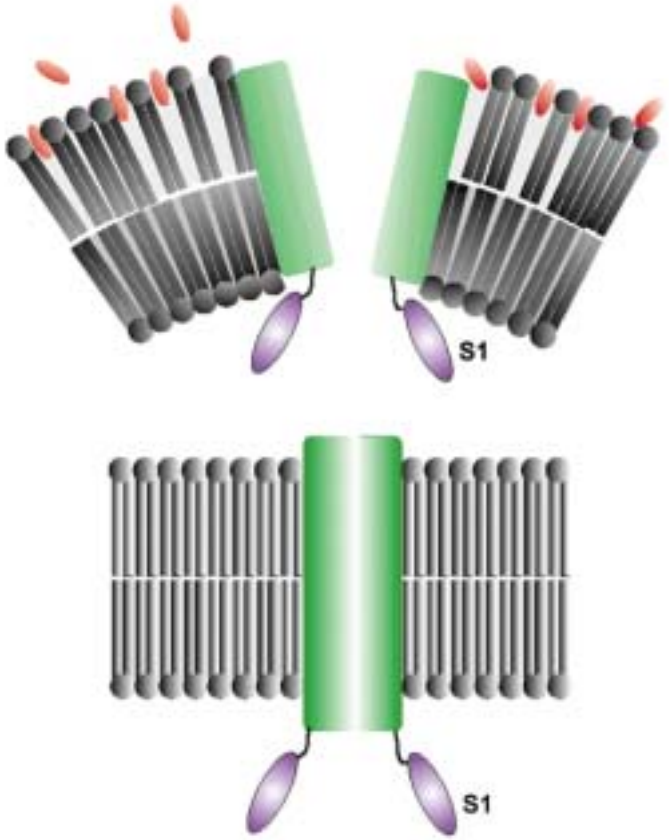
- **Gruner, *PNAS*, 82 (1985) 3665.**
- **Gruner, in *Biologically Inspired Physics* (Peliti, ed., Plenum, 1991)**

# Question #5:

## Do membrane proteins work in a qualitatively different way than aqueously soluble proteins? How, and to what extent, does Nature use distributed physical fields to modulate protein function?

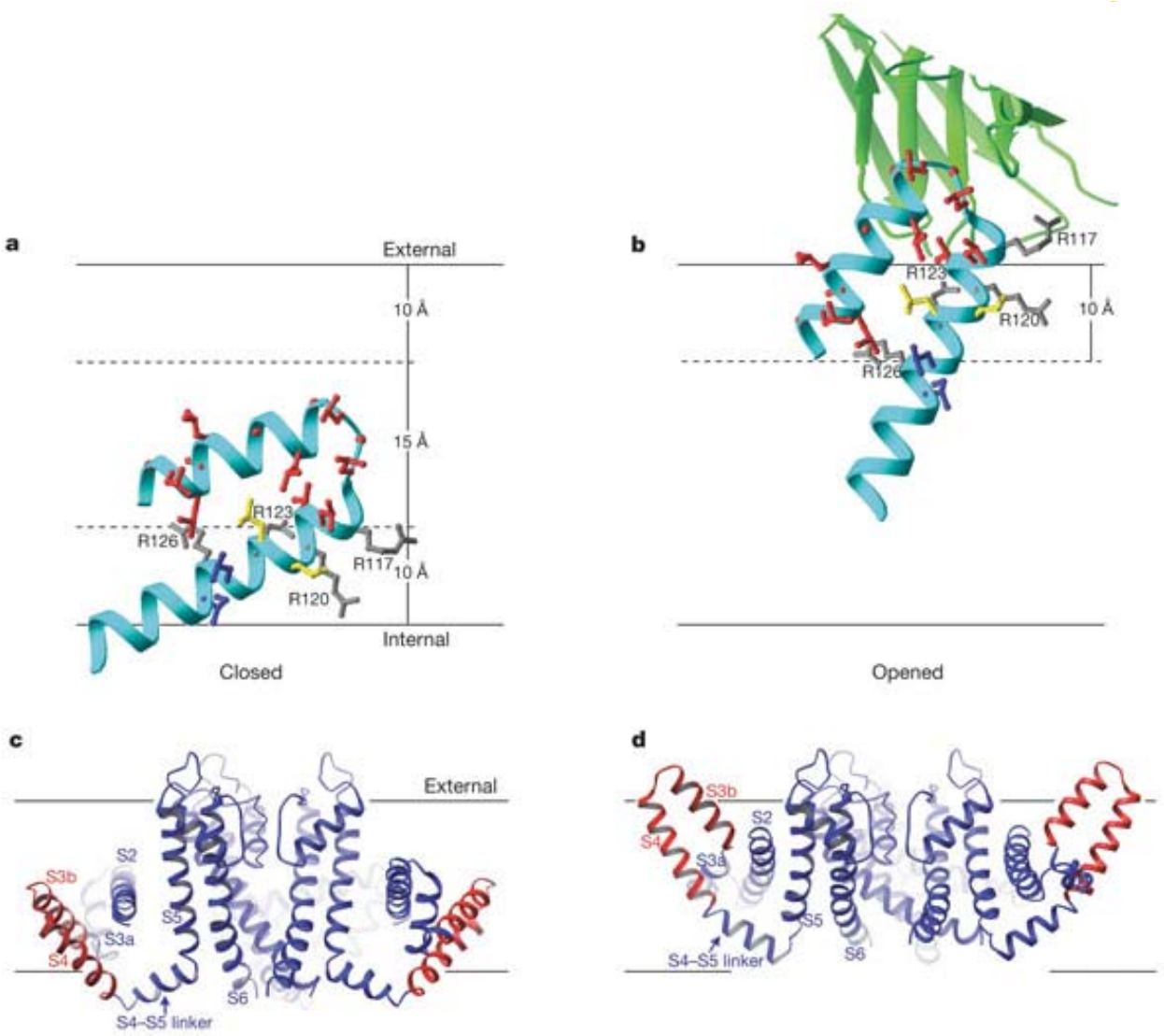
- Embedded in anisotropic medium
- Subject to anisotropic electric and elastic fields

# Distributed Field-activation I: Mechanical




## Mechano-activated channels

From F. Sachs




# Electric Field activated channels

From MacKinnon

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# ...which leads us to...

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## Question #6:

**What are the structures of membrane proteins?**

**What are the structure-function relationships unique to the membrane environement?**

# The questions go on....

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## Question #7:

**Symmetric lipid bilayers are never found in biomembranes. What are the phase properties, distributed fields, and effects on proteins of asymmetric lipid bilayers?**

# ...and on....

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## Question #8:

**Recent work on "lipid rafts" has demonstrated in-plane coexistence of lipid patches of different compositions. What are the phase properties and effects on proteins?**

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# ...and on, and on....

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## Question #9:

## Question #10:

## Question #11:

## Question #12:

## Question #13:

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**X-rays alone won't provide the answers to these questions – the best information comes from combining different experimental approaches.**

**But it is clear that many x-ray techniques, in the future as in the past, will be at the forefront in investigating these questions.**

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# END